Polant and Tradement Office: U.S. DEPARTMENT OF COMMERCE
Under the Papareent Reduction Act 1995, my parsons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)				
	In re Application o	•		
PHUVEOSED DY	Queen El. Al.			
SEP 3 Brid	Application Number Filed			
FIU	310252 2/13/89		2/13/89	
	Group Art Unit	Examiner		
Assistant Commissioner for Patents Washington, DC 20231		Pa	per No. #/6	
I hereby request access under 37 CFR 1.14(a identified ABANDONED application, which is: (A) referred to in United States Patent Nu (B) referred to in an application that is op Application No.	(CHECK ONE) umber <u>553</u> en to public inspe	ction as set forti	, column, n in 37 CFR 1.11, i.e.,	
paper number		, filed	l, or	
Please direct any correspondence concerning this request to the following address:				
Signature Signature Typed or printed name		POR PTO U Approved b Unit:	$-A \cdot B$	

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Weshington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Weshington, DC 20231.

055530101A

United States Patent [19]

Queen et al.

[11] Patent Number:

5,530,101

[45] Date of Patent:

Jun. 25, 1996

[54] HUMANIZED IMMUNOGLOBULINS

[75] Inventors: Cary L. Queen, Los Altos; Harold E. Selick, Belmont, both of Calif.

[73] Assignee: Protein Design Labs, Inc., Mountain View, Calif.

[21] Appl. No.: 634,278

[22] Filed: Dec. 19, 1990

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 590,274, Sep. 28, 1990, abandoned, and a continuation-in-part of Ser. No. 310,252, Feb. 13, 1989, abandoned, which is a continuation-in-part of Ser. No. 290,975, Dec. 28, 1988, abandoned.

[51] Int. CL⁶ A61K 39/395; C07K 16/28

[58] Field of Search 424/85.8, 133.1, 424/143.1; 530/387, 388.22, 387.1, 387.3

[56] References Cited

U.S. PATENT DOCUMENTS

4,816,397 4,816,567	3/1989	Boss et al
		Geers et al
5,225,539	7/1993	Winter.

FOREIGN PATENT DOCUMENTS

2/1986 European Pat. Off. . 0171496 3/1986 European Pat. Off. . 0173494 6/1986 European Pat. Off. . 0184187 9/1987 European Pat. Off. . 0239400 6/1988 European Pat. Off. . 0266663 2188941 10/1987 United Kingdom. 9/1986 WIPO. WO86/05513 WIPO. WO87/02671 5/1987 WO89/01783 3/1989 WIPO.

OTHER PUBLICATIONS

Vitteta et al., "Redesigning Nature's Poisons to Create Anti-Tumor Reagents," Science 238:1098-1104 (1987). Ellison et al., "The nucleotide sequence of a human immunoglobulin C(gamma), gene", Nucleic Acids Res. 10:4071-(1982).

Hieter et al., "Cloned Human and Mouse Kappa Immunoglobulin Constatn and J Region Genes Conserve homology in Functional Segments", Cell 22:197-207 (1980).

Sharon et al., "Expression of a V_HC_K chimaeric protein in mouse myeloma cells", Nature 309:364-367 (1984).

Takeda et al., "Construction of chimaeric processed immunoglobulin genes containing mouse variable and human constant region sequences", Nature 314:452-454 (1985).

Tan et al., "A Human-Mouse Chimeric Immunoglobulin Gene with a Human Variable Region is Expressed in Mouse Myeloma Cells", J. Immunol. 135:3564-3567 (1985).

Morrison et al., "Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains," *Proc. Natl. Acad. Sci.* 81:6851-6859 (1984).

Boulianne et al., "Production of functional chimeric mouse/ human antibody," *Nature* 312:643-646 (1984).

Neuberger et al., "A hapten-specific chimeric IgE antibody with human physiological effector function," *Nature* 314:268-270 (1985).

Morrison, S. L., "Transfectomas Provide Novel Chimeric Antibodies," Science 229:1202-1207 (1985).

Sahagan et al., "A Genetically Engineered Murine/Human Chimeric Antibody Retains Specificity for Human Tumor-Associated Antigen", *J. Immunol.* 137:1066-1074 (1986). Liu et al., "Expression of mouse::human immunoglobulin heavy-chain cDNA in lymphoid cells", *Gene* 54:33-40 (1987).

Better et al., "Escherichia coli Secretion of an Active Chimeric Antibody Fragment", Science 240:1041-1043 (1988).

Waldmann, T. A., "The Structure, Function, and Expression of Interleukin-2 Receptors on Normal and Malignant Lymphocytes," *Science* 232:727-732 (1986).

Leonard et al., "The human receptor for T-cell growth factor," J. Biol. Chem. 260:1872-1880 (1985).

Farrar, J., "The biochemistry, biology, and role of interleukin-2 in the induction of cytotoxic T cell and antibodyforming B cell receptors," *Immunol. Rev.* 63:129-166 (1982).

Greene et al., "Growth of Human T Lymphocytes: An Analysis of Interleukin 2 and Its Cellular receptor", in *Progress in Hematology XIV*, E. Brown ed., Grune and Statton, New York (1986) pp. 283-301.

Verhoyen et al., "Reshaping Human Antibodies: Grafting an Antilysozyme Activity", Science 239:1534-1536 (1988). Jones et al., "Replacing the complementarity-determining

regions in a human antibody with those from a mouse", Nature 321:522-525 (1986).

Hale et al., "Remission Induction in Non-Hodgkin Lymphoma with Reshaped Human Monoclonal Antibody CAMPATH-1H", Lancet Dec. 17, 1988, pp. 1394-1399. Chothia, C. and A. M. Lesk, "Canonical Structures for the Hypervariable Regions of Immunoglobulins", J. Mol. Biol. 196:901-917 (1987).

(List continued on next page.)

Primary Examiner—Lila Feisce
Attorney, Agent, or Firm—Townsend and Townsend and
Crew

[57] ABSTRACT

Novel methods for producing, and compositions of, humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin are provided. Each humanized immunoglobulin chain will usually comprise, in addition to the CDR's, amino acids from the donor immunoglobulin framework that are, e.g., capable of interacting with the CDR's to effect binding affinity, such as one or more amino acids which are immediately adjacent to a CDR in the donor immunoglobulin or those within about 3 A as predicted by molecular modeling. The heavy and light chains may each be designed by using any one or all of various position criteria. When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen, such as a protein or other compound containing an epitope.

13 Claims, 55 Drawing Sheets